## REMARKS

The Rejection of March 10, 2004 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for his thorough and detailed remarks in the most recent Office Action and the entrance of Applicant's provisional election pursuant to the telephonic interview on February 2, 2004submission filed on 6/13/02. More specifically, Applicants thank the Examiner for his substantial effort in trying to move the claims to allowance given the prior art. Claims 9, 13-20, 24-31, 35-42, 47-55, 59-66 and 70-76 are currently pending. Claims 9, 20, 30, 42, 55 and 66 are amended herein. Claims 1-12, 21-23, 31-34, 43-46, 56-58, 67-69, and 77-84 are canceled herein. No claims have been added herein.

**Restriction Requirement & Filing of Divisional**

In reply to the Restriction Requirement in the Office Action mailed March 10, 2004 and in connection with the above identified patent application, Applicant hereby formally elects to continue the prosecution of claims 9-76 drawn to methods of producing a MSP-1 protein in the milk of a transgenic non-human mammal, identified as the claims of Group 1. Pursuant to a telephonic interview on February 12, 2004 this election is made without traverse, and Applicants have, in this action, cancelled claims 77-84. However, Applicant retains the right to file a divisional application covering the non-elected invention and the resulting cancelled claims. Given the remarks and amendments made herein it is respectfully proposed that this application is now in condition for allowance. An early and favorable consideration on the merits is earnestly solicited.

**Priority Claim**

The current application has been amended to recite that it is indeed a division of U.S. patent application No. 09/175,684. Therefore, Applicant is in compliance with 35 USC § 120, and the Examiner's objection based thereon is respectfully overcome.

**Applicant Recognition of the Level of Ordinary Skill in the Art**

Applicant again recognizes that the level of ordinary skill in the art concerning the instant claims is high. This is important in the instant matter as it is supported by the requirement of an understanding of the different abilities, strengths, weaknesses and effects of various protein expression systems, particularly with regard to developing transgenic animal expression systems capable of producing exogenous proteins of interest and the time required to build a herd of transgenic animals according to the prior art.

Applicant respectfully also points to relevant and recent legal precedent in the biotechnology arena to make the case that the expected level of skill in the art is high. Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999); Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882). What this means in practical terms is that the specification is not required to teach every detail of the invention or to perform the function of a technical production manual/specification on a species-by-species basis in order to exemplify the recitations of claims for non-human mammals. The specification need only explain how to make and use the invention within a practical example (e.g., transgenic mice) without requiring an inordinate amount of experimentation or reams of data showing multiple levels of exemplification each desirable production species. The fact that experimentation needed may be complex or even repetitive does not necessarily make it undue if a person skilled in the art typically engages in such experimentation, as in the instant field. In re Borkowski, 422 F.2d 904, 164 USPQ 214 (CCPA 1970). Applicants therefore believe that the teachings provided in the specification allow those skilled in the art to practice the invention as recited in the pending claims, and that the invention as claimed has been reduced to practice. Hybritech Inc., v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986).

**Sequence Listings**

In compliance with 37 CFR §§ 1.821 - 1.825 applicants attach the appropriate computer readable form of the Sequence Listing as well as a paper copy of the Sequence Listing accompanied by an Amendment directing its entry into the specification. Respectfully, this

rejection is overcome. Applicant should also point out that the claims as amended only recite sequence information for modified nucleic acid sequences. That is, the Applicants have modified the nucleic acid sequences without modifying the amino acid sequence of the protozoan protein – for the purposes of a vaccine against malaria the amino acid sequence needed to remain as close to the wild-type as possible. Applicants thank the Examiner for his diligence in continuing the examination of the claims on the merits even though electronic copies of all the amino acid sequences presented in the Figures had not been made.

**Declaration**

See attached declaration of Dr. Harry Meade and partial *curriculum vitae*.

**Acknowledgement of Allowability**

On pages 16 and 17, of the Office Action of March 10, 2004 the Examiner has acknowledged the allowability of claims generally when some modifications/amendments made to the existing claims 9-76 relative to the existing prior art provided and the record to date. This response has been an attempt to move claims 9-76 into compliance and condition for allowance. If the Examiner has any suggestions how this may be achieved that were not included in this response, or believes for any other reason that direct contact with Applicants' attorney would advance the prosecution of the case to finality, he is invited to telephone the undersigned at the number given below.

**The Rejection Under 35 U.S.C. §112, first paragraph**

Claims 9, 13-20, 24-31, 35-42, 47-55, 59-66 and 70-76 stand rejected under 35 U.S.C. §112, first paragraph for failure to enable a person skilled in the art to perform the invention commensurate with the breadth of the claims. This rejection of the claims, as amended, is respectfully traversed.

The test for claim support under the first paragraph of 35 U.S.C. § 112, is whether the disclosure as originally filed reasonably conveys to the artisan that the inventor had possession at

the time of the later claimed subject matter, rather than the presence or absence of literal support. Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 227 U.S.P.Q. 177 (Fed Cir. 1985); In re Kaslow, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed Cir. 1983). As has been previously stated by the courts:

> "Enablement is a legal issue. The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art." *In re Myers*, 410 F.2d 420, 161 USPQ 668 (CCPA 1969); *and see, Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co.*, 221 U.S.P.Q. 481 (Fed. Cir. 1984).

More to the point, the issue of adequate enablement depends on whether one skilled in the art could reproduce the claimed invention without "undue experimentation." *See,* Wang Labs, Inc. v. Toshiba Corp., 993 F.2d 858, 26 U.S.P.Q.2d 1601 (Fed Cir. 1993); Utter v Hiraga, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988). The standard in this inquiry was supplied by the Federal Circuit when that court announced that enablement by a disclosure is not precluded even if some experimentation is required, the only limiting factor is that this experimentation must not be "undue." In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In *Wands* Judge Smith decided that the key word in this formula is "undue" not "experimentation" and applied a reasonableness standard, given the nature of the invention and the state of the art when he stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is **merely routine**, or if the specification in question provides **a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.**" *Wands* at 737 (emphasis added).

Given the above, therefore, it must be understood that when the Applicants, as in the instant specification:

provide a working example in a transgenic system (mouse);

detail the benefits and methods of optimizing a given nucleic acid sequence for expression in terms of AT composition in a mammalian transgenic system;

provide a workable means for the removal or replacement of AUUUA mRNA instability motifs,

indicate and then proceed to make specific mutations to overcome mammalian glycosylation issues;

provide extensive guidance to appropriate protocols throughout the specification – including references to old, well-known, and well understood laboratory protocols;

reference many relevant citations in the literature; and

then - **actually produce the exemplary protein in high concentrations in a transgenic animal;** any experimentation that may be necessary, becomes routine.

The practitioner in the field no longer need worry that a certain parasite molecule, like the one derived from *Plasmodium falciparum* and claimed in the instant specification, can be made and expressed in the milk of a transgenic animal, it is known to a certainty that it will. The working example of the current invention produced by the Applicants provides this assurance, and makes irrelevant the difficulties that an inexperienced practitioner may have in referencing the appropriate protocol.

More to the point, many of the characteristics of the MSP-1 protein as well as the DNA and amino acid sequences of *Plasmodium falciparum* as well as other parasites and other parasite proteins are well known by artisans in the field and may be employed in the effort to optimize selected proteins for expression in mammalian transgenic systems. The method of Applicants and the purpose of the application announces provides a means of making proteins that otherwise cannot be made, or cannot be made in amounts adequate to address and service dire need for critical vaccines around the world.

It is much appreciated that the Examiner has worked diligently to review the prior art and to aid Applicant in moving the claims toward allowance. However, a remaining objection on the part of the Examiner unnecessarily restricts the appropriate scope the claims. This is the Examiner's suggestion that more literal exemplification may be needed to fully enable the current invention, and corresponding claims, for the *genus* of non-human mammals rather than just the species of *mus musculus* (mouse). Given the above argument, standing alone, Applicant believes that this objection is overcome. However, Applicant also provides a declaration from Dr. Harry Meade to the effect that the innovations made for the current invention are indeed applicable across the spectrum of non-human mammals. In fact, Dr. Meade is one of the world's leading experts on transgenics generally and specifically within the field of exogenous recombinant protein production in transgenic mammalian systems. In the

transgenics field the mouse is an experimental model used to develop molecules and genetic constructs for insertion in other 'production' animals. In this sense transgenic mice are "benchtop" mini bio-reactors used to quickly finetune the inventions made by scientists like Dr. Meade before they are inserted in "production models" such as goats, cattle, sheep, pigs or rabbits for "scale-up." In addition to having mammary glands that work on the same principle, amenable to the same hormonal manipulation and accessible to the same milk purification methods, transgenic mice are created using almost identical techniques to those used for the creation of larger mammals.

Applicants believe that the novelty and enablement of the current invention lies within the innovation of using transgenic production methods to produce a protozoan protein that many in the scientific realm (Ex: bacterial production in *E.Coli*) had simply despaired of producing in any meaningful quantities or with any appreciable amount of bioactivity. The Applicants overcame these prior art problems not only with the use of the transgenics platform and the production of a hard to express protein sequence(s) from the milk of transgenic mammals but with the insight and skill to manipulate the nucleic acid sequence of the relevant *Plasmodium falciparum* sequence so that it would: (1) remain true to the amino acid sequence of the actual *plasmodium* protein while being much more amenable to production and secretion; and, (2) altering the glycosylation sites of the target protozoan sequence such that its glycosylation would be limited to better enable the production of an effective vaccine for malaria as against actual challenge from a disease carrying organism. This had not been done previously, and offers the realistic hope of an effective malaria vaccine. The initial work on this invention was done in mice, as they are the common model for this field and the most amenable to rapid scientific research. The reduction to practice for mice and other non-human mammals was thus complete with the filing of the original parent application. To provide a stronger foundation for the contemporaneous prior art (i.e., each is pre-1997) and the exemplication of the field generally, Applicant points to the five citations provided below. Each provides the use of a different transgenic mammal developed through very similar cloning techniques for the production of a variety of protein(s) of interest and each serves to underscore the fact that the work the inventors did in mice was and is applicable across all non-human mammals. (Sheep, Rats, Mice, Pigs and Goats).

1. Carver A, et al., ***Expression Of Human Alpha 1 Antitrypsin In Transgenic Sheep***, CYTOTECHNOLOGY. 1992;9(1-3):77-84.

2. Hirabayashi M, et al., ***Transgene Expression In Mammary Glands Of Newborn Rats***, MOL REPROD DEV. 1996 Feb;43(2):145-9.

3. Prunkard D, et al., ***High-Level Expression Of Recombinant Human Fibrinogen In The Milk Of Transgenic Mice***, NAT BIOTECHNOL. 1996 Jul;14(7):867-71.

4. Van Cott KE, et al., ***Affinity Purification Of Biologically Active And Inactive Forms Of Recombinant Human Protein C Produced In Porcine Mammary Gland***, J MOL RECOGNIT. 1996 Sep-Dec;9(5-6):407-14.

5. Ziomek CA., ***Minimization Of Viral Contamination In Human Pharmaceuticals Produced In The Milk Of Transgenic Goats,*** DEV BIOL STAND. 1996;88:265-8. **GENZYME TRANSGENICS CORPORATION** (GTC), Framingham, MA, USA.

The protocols disclosed in the specification, provide the public the ability to practice the invention, essentially by providing a detailed map leading towards a goal that has already been reached, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field and the contemporaneous prior art, some of which is cited above, it is clear that the specification, as tempered by the relevant case law discussed above, does enable other workers in the field to make and use the invention without "excessive" experimentation. Wands at 740.

Indeed, the application presents multiple protocols, all well known, that provide for the isolation of the relevant nucleic acid sequences and then provides not only the motivation to optimize them but methods to make sure that decisions taken will also allow the expression system so modified to work in transgenic mammals. This level of disclosure is **more than** what is necessary for a specification to provide. In determining whether the disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, U.S. patents, and old well-known laboratory protocols. Therefore, the Examiners rejection of the claims under 35 U.S.C. § 112, first paragraph, is through the amendments made to the claims and the remarks herein traversed, and reconsideration of the claims is, respectfully, requested.

**The Rejection Under 35 U.S.C. §112, second paragraph**

Claims 9, 13-20, 24-31, 35-42, 47-55, 59-66 and 70-76 stand rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed. Each of the rejections enunciated by the Examiner under 35 U.S.C. §112, second paragraph have been addressed through specific amendment to each of the relevant claims, particularly to the underlying base claims. The amendments were made to clarify, particularly point out, and distinctly claim the subject matter of the invention along the guidelines of what the Examiner noted as enabled in the last action. Many previously rejected claims were cancelled pursuant to this action. Reconsideration of the rejection of amended claims 9, 13-20, 24-31, 35-42, 47-55, 59-66 and 70-76 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

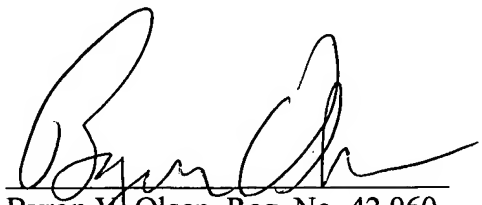
Other than a fee for the extension of time no fee is deemed necessary in connection with the filing of this Amendment after Final Rejection. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 9/10/04

By: 

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